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Episode 45: Under attack: Sepsis and patient safety in the age of antibiotic resistance

Josh Casey: Hi, I'm Josh Casey. Welcome to QuidelOrtho Science Bytes, your trusted source for diagnostic insights and innovations. March 9th marks the start of Patient Safety Week for 2025. In this episode, we're putting the spotlight on sepsis and how healthcare providers can recognize, treat and monitor infections sooner, including protocols to help prevent the spread of antibiotic resistance in the community and among hospitalized patients. According to the U.S. Centers for Disease Control and Prevention, sepsis was a leading cause of death in U.S. hospitals in 2024, affecting at least 1.7 million patients nationwide, with 350,000 succumbing to infection. What's more shocking than these statistics is that experts believe more than 80% of sepsis deaths can be prevented if identified and treated in time. Joining us today for this important discussion is Mike Broyles, Doctor of pharmacy and director of medical affairs for biomarkers at Thermo Fisher Scientific. With more than 30 years of experience as a hospital pharmacy and laboratory director, Dr. Broyles is a leading expert on sepsis and the clinical use of drugs with a focus on antimicrobial stewardship. Prior to joining Thermo Fisher Scientific, Dr. Broyles was a consultant for over 25 years working with a large independent hospital network as pharmacy advisor chairman focused on developing and implementing hospital-wide clinical initiatives. Dr. Broyles has worked passionately throughout his career to define effective protocols and decision support processes in patient management and the use of diagnostic technology to help clinicians improve outcomes through better clinical care. We're so fortunate to have Mike here with us today to recognize Patient Safety Week and share his expertise with us. Welcome, Mike. Thank you for joining us.

Mike Broyles: Hey, Josh, so glad to be here and have a little time to discuss this very important topic.

Josh Casey: Great, excellent, thank you. So, to set the context for today's conversation, can you please give a brief overview of sepsis? How do patients typically contract it? What are some of the presenting signs and symptoms, and the pathophysiology of the disease? It's my understanding that most sepsis cases are caused by bacterial infections, is that right?

Mike Broyles: So, sepsis is really a dysregulated immune response to infection. It's life-threatening and it's an exaggerated response that leads to organ dysfunction. It can result in shock, multiple organ failure and death. Patients typically don't contract sepsis. What they do is they contract the infection, and then they react to the infection stimulus. So, the greater the degree of infection or the more infection they have, the more likely a patient is to develop sepsis. So, to make it very clear, the chances of sepsis are in proportion to the degree of infection. Now, the symptoms can be varied. You can actually have symptoms that can, where you actually have fever or you can have low temperatures, hypothermia. Typically, you have tachycardia or fast heart rate, fast breathing rate. Often we see confusion or altered mental status. Typically, there's body pain, the patient may be sweaty or cold and clammy. Uh, typically in the later stages, we see decreased urine output, and these are kind of some of the more common presenting symptoms. Now, as far as the pathophysiology is of sepsis, this is kind of complicated. There's kind of like four stages. I'll kind of lead you through that. It's kind of like what I would suggest is initiation and then we have what we call the cytokine release, which then causes the inflammation and the organ dysfunction. So as far as the initiation, this begins when the infectious agent triggers an immune response. So this is kind of complicated, but I'll just try to make this very simple. The response is initiated by what we call pathogen associated molecular patterns or PAMPs, P-A-M-P-s, which are found on the surface of pathogens. So, this is bacteria, viruses and fungi. And then we have what we call damage-

associated molecular pathogens or patterns, which is DAMPs, these released from the actual damaged tissue. So then, the molecules of the active pattern recognition receptors, they activate things within the body and particularly what we call the TLR, the to like receptors, of which we know there's more than a dozen types. And these are on the immune cells such as the antigen presenting cells and then the monocytes. So all that probably the one thing that most clinicians are familiar with is the monocytes, which is part of the white cell response. And so it's interesting that this actual stimulation of to receptor, which is so very important, is what we'll discuss in a minute, which is the part which bacteria activates and then causes these cells to actually make procalcitonin. The next phase is actually what we call the cytokine release. So it's activation of these toll receptors and this is kind of like a branching out. So, you have the trunk and you have the branches and it gets more and more. So, we started with the trunk and now we're on the branches. So it's activation of the toll-like receptors then causes what we call pro-inflammatory cytokines. And then this causes the release of human necrosis factor alpha, interleukin 1, interleukin 6 and interleukin 12, and then the interferons. Then this causes widespread inflammation throughout the body. Now, it's very important to note that this is what happens in any type of infection, and these cytokines are essential for fighting infection. It's just when you get this excessive release, this exaggerated response, that can lead to tissue damage and contribute to the manifestations of sepsis. It's kind alike when a patient has allergies. Now you've seen an antigen, but they have an exaggerated response, and this is what we see in this situation. Now, the next piece is what we call the inflammation of the coagulation component. So the inflammatory response activates the coagulation cascade, and you have these pro-inflammatory cytokines actually stimulate clotting factors. Well, the stimulated clotting factors then lead to a microvascular clot formation, which then impairs blood flow to the organs and tissues resulting in ischemia and further organ dysfunction. So once that starts, then we have the downstream effect, which is the organ dysfunction. And as sepsis progresses, it can lead to severe organ dysfunction causing alteration in hemodynamics, the metabolism and cellular function. So, most commonly this affects the lungs, which is where we have the adult respiratory distress syndrome, which you often hear as ARDS. We have the effects of the kidneys, the kidneys begin to quote shut down, as does the liver and the cardiovascular system then develops shock. We get this low blood pressure. So when all these organs are affected, then we get multi-organ dysfunction or what we call MODs, which is a very critical indicator of severe sepsis. This then manifests and then the signs and symptoms that we talked about other. So that's kind of like the pathophysiology. And so you're correct, it's, you know, as far as, you know, sepsis cases are generally bacterial. At least 80% of sepsis is bacterial, and it can vary somewhat by geographical location, but viral and fungal etiologies are the most common methods.

Josh Casey: Great. Thank you for that explanation. So at the start of the conversation today, I mentioned a few stark and startling statistics from the CDC about the impact of sepsis. Are we seeing an increase in cases now? How did it become such a threat to patient safety?

Mike Broyles: Yes, so absolutely for sure the rate is continuing to increase. It's steadily you can see it climb each year by year. And the interesting thing is, even though we try to diagnose sooner and we try to treat earlier, it still continues to grow. Some of these reasons, there's a variety of reasons, so, some of these include the aging population, the fact that we are now using more immunosuppressive therapies. If you look on TV and you see all these drug ads out there, you see the end in the term MAB. The ones that they use for many things. All of those are immunosuppressive therapies, so we see a lot of that. We have more invasive procedures and we have the spread of multi-drug-resistant pathogens. So as these pathogens become more resistant then Sepsis continues to grow. The other thing is, is that we're

actually recognizing more cases of sepsis. So the fact that we actually recognized sepsis where before we probably didn't, that allows the numbers to continue to grow also.

Josh Casey: OK. So, the ability to count more cases is certainly contributing, but it sounds like there's a number of factors there, including, uh, there's, there's no coincidence that the rise in sepsis cases, we, we've also seen an increase in antibiotic resistance. Can you talk a little bit about the connection there and maybe explain what some of the consequences of antibiotic resistance are?

Mike Broyles: Yeah, so many, OK. The consequences of antibiotic resistance are varied. So, number one is we see the overall increase incidence of sepsis, which just makes sense. You know, we have more infection out there, it's more difficult to treat. So that's a logical progression. The other thing is, is that that then requires more complicated treatment protocols. So we're using more less effective treatment or sometimes combinations of agents, and then we're using more toxic antibiotic choices than we did before. This then results in higher mortality rates, so the death rate is higher. And then here's the other thing that people never consider. There's the morbidity, OK? There's the quality of life, and let me give you an example. So it's estimated by the year 2050 if we continue to do like we do now, multi-drug resistant infections will be the leading cause of death globally, and that will result between somewhere between, well, estimated 20 to 30 million patients per year. And so that's the death, but here's the other thing that you don't think about, morbidity. So, let's say for instance, I'm out working in the yard, I get a cut or scratch on my leg and I develop sepsis. Well, I may not die, but I could end up losing a limb. So there's the morbidity that's associated with that. So that's always a cause for concern. The other thing that you have is prolonged hospital stays, you have increased healthcare costs, and then one of the things that people never think about is, is that this leads to an impaired immune response. Antibiotic resistance leads to recurrent infections and prolonged illness then may impair the immune system, and this can be due to a number of reasons, but in particular the microbiome. So then this immunosuppression then exacerbates the severity of sepsis and you've actually started this vicious cycle, this increased incidence of opportunistic pathogens. So it kind of basically propagates itself and then there's the diagnosis of the multi-drug resistant organisms and there's susceptibility profiles that continue to change and again start this cycle, making it more difficult to treat patients.

Josh Casey: So it's, so it's a compounding problem for sure. So we know an important tool in the fight against sepsis is the biomarker procalcitonin or PCT. Can you talk a little bit about the diagnostic utility of PCT? What it measures, how clinicians can use it and interpretation of results?

Mike Broyles: Yeah, this is a great question. So, what we call procalcitonin, some people call it proCAL or PCT, it helps in the early detection of bacterial infection. It's very, very important. And I'll discuss this kind of as we go through this, this talk. It can also help in the differentiation of non-infectious inflammation versus infectious inflammation and most importantly in that differentiation of a viral versus a bacterial infection because obviously we're not going to give antibiotics in that viral patient. The other thing that's often not considered is its ability to assess the severity of the bacterial infection, which is very important, which then helps in the prognosis. So for instance, if I give you an example, somebody came in with sepsis and they had a PCT of say 2 versus a PCT of say 30 or 40, how I interpret the severity of that bacterial burden is much, much different. Talk a little bit more about that, but it's very important to understand that. And so then when you think about how should we order, PCT should be ordered on admission in the ED when other tests or procedures for infection or sepsis are ordered. I mean, we just do that when we do all the others. And so then what it is actually telling us is, is there actually a bacterial

burden at this point in time, and that provides a value. Obviously, it's prognostic when these PCT values get very, very high, the cost, the concern for mortality is also very, very high. The other thing it does is it provides a baseline for the next serial measurement because this is not a one and done test. So we're going to do a baseline, we're going to get one at 24 hours to evaluate therapy, and then we can get a third one to determine when to actually safely stop antibiotics. And so when we get that second PCT test, what it's actually telling us is, are my antibiotics working? And then if it's not working, that gives us the opportunity to change and then the other piece is when can we safely stop. So the other thing to think about is, so as long as that infection has been present for 6 or more hours, which is almost everyone who comes to the ED who's been, you know, who will be ill enough for treatment, you'll have a snapshot point in time about the amount of bacteria that's present and if that actually has become systemic. So our normal procalcitonin level is 0.5 to 0.1 nanograms per mL. And then we generally would say anywhere from 0.1 to 0.5 is considered a localized infection, so it hasn't spread. And then anything above that becomes systemic. Most hospitals will use 2 as an alert value and 10 is a critical value. So alert value means that lab is going to call someone at the nursing station or someone and say, OK, here's the issue. And then a critical value would be when you actually contact the provider and say, OK, there's something wrong. Now values as high as 1,000 have been recorded, but when you get these very high values, it's very, very concerning that that patient has a very poor prognosis. So, failure of PCT to decline is also prognostic. So if it does not decline by 50% over the next 96 hours, that demonstrates an increased mortality rate of 50%. So monitoring the decline of PCT is very important in the assessment of therapy.

Josh Casey: So, in addition to determining which patients are at risk of sepsis from bacterial infection, you know, as a confirmatory test and, and monitoring the effect of antibiotic therapy, can PCT also help clinicians identify specific infection or determine which class of antibiotics would be most effective in any given patient situation?

Mike Broyles: Yeah, so this needs a little bit of discussion if that's OK. I'd like to give you just a little bit of background information. So, as I mentioned earlier, it's only triggered by bacteria, OK? So PCT is never elevated in pure viral infection. And so the nice thing is, is it rises very rapidly within 3 to 6 hours once that toll-like receptor is affected by bacteria. Now, the other thing is very nice is it's time to peak is 24 hours. So for as far as from the stewardship standpoint, evaluating patients, that's very important. And then thirdly, it's also very nice in that it's elimination half-life is also 24 hours, which is perfect to, to evaluate the effectiveness of therapy. And by that I mean is that if PCT was say 10 today I had appropriate therapy, tomorrow I'd expect it to go from 10 to 5, the next day from 5 to 2.5 and so on. So it's extremely helpful in helping us understand what is happening. With antibiotics, OK, it's, it's incredibly important. Now, the other thing is, is that as approved by the FDA in many circumstances when you have an absolute value of 0.25 or lower respiratory tract infections or 0.5 in sepsis or an 80% reduction from your maximum value. OK, so for instance, if it was 10, I multiply 10 times 0.2, that's the 80% reduction if PCT got to be 2 I can then safely stop. Now the beauty of this is huge. So instead of giving somebody a fixed duration of antibiotics like 5 days, 7 days, 10 days. The nice thing about this is that every response that you get is titrated that patient which takes into account their immune system, the types of antibiotics, the types of infection, and so overall, they have a better, higher quality of care, but their exposure to antibiotics is much less, OK? So it's very, very important, OK, to understand that. So the serial measurement then is very important in knowing when you can safely stop antibiotics. And that's one of the things I would like to drive home is, is that more antibiotics is not better. I mean, more is

better if you want to pay me more, give me more time off, give me more dessert, whatever the case may be, but more is not better with antibiotics and it's actually been shown that's not the case. The other thing to think about is microbiologic cure is always the head of what we call radiographic and clinical cure. So if you're waiting on those, you've actually killed the bacteria off and they're long gone, waiting on this response. So PCT can help a lot with that. Now, the other piece that's very important is PCT can't help you understand the class of antibiotic therapy, but this monitoring in 24 hours will tell you if the prescribed therapy is working as you expect it to be when you see that 50% reduction. So the key then is evaluating therapy before that patient becomes critically ill. So if I have a patient who's on inappropriate therapy, I started them on what I thought is the right therapy, and it turns out it wasn't, PCT will go up. It'll give me a chance to change that therapy before they get bad, and that's the key, what is, in, you know, clinically we say before that patient crashes. And so that's kind of the key concept. If that PCT goes up, I change therapy, then I re-evaluate it. If PCTs go down, I can feel very comfortable about that therapy. So, extremely useful in managing our patients.

Josh Casey: So what other ways does PCT play an important role in establishing an effective antibiotic stewardship program? What additional strategies do hospitals need to consider to limit the overuse of antibiotics and mitigate the effects of antibiotic resistance?

Mike Broyles: So this is one of the most often overlooked considerations in the use of antibiotics and sepsis. Think about this. When sepsis is suspected, clinicians were always going to initiate antibiotics because they're in that just to be sure timeframe, that mindset that says, OK, I've got to start antibiotics just for sure because the consequences that the patient needed antibiotics and didn't get them is critical and that's part of the guidelines. We're good with that. However, think about this. Based on the current uh sepsis screening criteria, 40% of the time when the criteria is met, it's later found that they don't have sepsis and the antibiotics were given needlessly. So, the suggestion would be then if that patient is clinically improved and you have a second normal PCT, why would you continue to give antibiotics? So what you actually see in situations like this where you have the suspected sepsis and you think it's bacterial, but it's not, you'll see a low normal PCT on admission. 24 hours later, you'll see a second low normal PCT. This is greater than a 99% probability that that patient does not have a bacterial infection which is so important, so it gives us the opportunity then to stop antibiotics. So, just to drive home at this point, I actually pulled this up and I'm just going to quote to you this PCT is an integral part of the surviving sepsis campaign guidelines. OK, quote, for sepsis or septic shock, inadequate source control uh where optimal duration of therapy is unclear, this is everyone. We don't know how long to treat them. Notice what this says. It says, we suggest using procalcitonin and clinical evaluation to decide when to discontinue antimicrobials over, quote, clinical evaluation alone. Very, very important. So secondly, PCT can be used to safely stop antibiotics and provide a patient-tailored duration. This is very, very important. Patient tailored versus a fixed duration. It's been repeatedly shown in hundreds of randomized controlled trials and real world studies that PCT is safer. It has fewer adverse events from drugs as you would expect. The *C. difficile* rate is lower, even 30 day readmissions and costs are significantly lower. So to be clear, what I just said is that you can safely use fewer antibiotics and have a better outcome. I mean, who wouldn't want that? I mean, if you think about it. So PCT should be part of all antimicrobial stewardship programs, but there's a caveat. It requires a lot of education. It has a lot of nuances that clinicians need to know. And there actually needs to be a strong process in place to make sure that the clinicians act on the results. No one wants to order a test and not get the benefit of it. So the key then is, is that there's a process in place. And historically, it's always been the best when it's part of a pharmacy

oversight, which is under the antimicrobial stewardship team. And they're reviewing the results and providing reminders to prescribers to act on PCP values. So without question, it will safely reduce antibiotic exposure when followed, OK? But you have to kind of get past this mindset that more is not better when you prescribe antibiotics. The correct amount, OK, for the correct duration is the key. So it's been just demonstrated that less is safe it's actually uh, more cost effective and it actually provides less harm to the patient. The interesting thing is that when clinicians try PCT aided protocols, they actually learn to understand the concept of bacterial burden and actually makes them feel more comfortable and they realize that their quality of care is actually better for their patients.

Josh Casey: That's excellent advice and something all our listeners can take to heart. But that's all the time we have for today. Thank you, Dr. Broyles, for joining us to share your insights on sepsis, patient safety, and antibiotic stewardship. I hope everyone enjoyed the conversation. Please be sure to review the sections and links within the podcast description. You can always go back and listen again if you'd like more details. Thank you all for listening in. If you haven't already, please subscribe to QuidelOrtho Science Bytes, our monthly podcast brought to you by QuidelOrtho Corporation, where we are transforming the power of diagnostics into a healthier future for all. Until next time, take care, everyone.